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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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09/255,397 02/22/99 SERBEDZIJA

G 18852-000500

EXAMINER

HM12/1025

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SHUKLA, R

ART UNIT

PAPER NUMBER

1632

DATE MAILED:

10/25/00

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

## Office Action Summary

Application No.

09/255,397

Applicant(s)

SERBEDZIJA ET AL.

Examiner

Ram R Shukla

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

### Status

- 1) ☐ Responsive to communication(s) filed on 11 August 2000.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-21, 43, and 54-90 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) 21, 54-74, 82, 84, 87, and 88 is/are allowed.
- 6) ☐ Claim(s) 1-20, 43, 75-81, 83, 85, 86, 89 and 90 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some \* c) ☐ None of the CERTIFIED copies of the priority documents have been:
1. ☐ received.
2. ☐ received in Application No. (Series Code / Serial Number) \_\_\_\_\_.
3. ☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

### Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 18) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other:

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### DETAILED ACTION

1. Amendment filed 8-11-2000 (paper #9) has been entered.
2. New claims 54-90 have been entered.
3. Amendment to claims 21 and 43 have been entered.
4. Claims 1-21, 43, and 54-90 have been entered.

### *Claim Rejections - 35 USC § 103*

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Amended claim 43 and new claims 75-79, 89, and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zikria et al (US 5,565,187, 10-15-96) in view of Shuo et al (WO9603034, 02-08-1996). LIA

Zikria et al teach methods for studying capillary circulation using fish fry and tadpoles wherein the toxic agent is injected into the yolk sac and the capillary circulation is observed (see the abstract and claims 1, 5, and 7). Zikria et al also teach that the method can be used for carrying out toxicological, pharmacological, physiological, embryological, oncological, pathological, etc. studies. In fact Zikria et al list a number of studies which have been used for toxicity studies, therapeutic studies and other studies using fish as the model system (see lines 24-61 in column 2). In column 4 -6, they also describe that the tail of the fish where the dye is injected is observed over time and based on the type of toxicological studies and the objective of the experiment, fish is exposed for various time periods and other parameters that can be changed. Zikria et al do not teach measuring mRNA or enzyme level for monitoring the effect of an agent whose toxicity is being studied.

Shuo et al teach a method of stably integrating a retroviral vector in the germ line of a fish to produce a transgenic fish which can be used for studying effects of mutation gene function (see last paragraph on page 6 continued in the first paragraph on page 7). Shuo et al also teach that zebrafish is ideal for embryological studies due to its transparent embryos (see

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last paragraph on page 3). Shuo et al also teach that different screens can be used for visual observation in a dissecting microscope, or by in-situ hybridization using gene probes for genes expressed in particular organs, using stains and antibodies or by injecting dyes, by functional screens, reporter gene expression assay, histochemical assays, immunohistochemical assays, enzymatic assays, RNA hybridization or RNase protection assays etc. can be used.

It would have been obvious to one of ordinary skill in the art to use a teleost for screening the toxicity of an agent in vivo by administering the agent to a teleost by the method of Zikria and detect the change in level of an enzyme or mRNA in one or more tissue or organs as taught by Shuo et al with a reasonable expectation of success. As taught by Shuo et al expression of a gene in fish can be monitored by any of the methods listed.

7. Previously presented claims 1-20 remain rejected and newly presented claims 80,81, 83, 85, and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stainier et al (Stainier DYR et al. Trends in Cardiovas. Medicine 4:207-212, 1994) in view of Driever et al (Driever et al Trends in Genetics. 10: 152-159, 1994), Weinstein et al (Weinstein BM et al. Nature Medicine 1:1143-1147, 1995), and Ozato et al (Ozato K et al. Cell Differentiation 19:237-244, 1986), for reasons of record set forth in the previous office action (paper #8).

It is noted that in the previous office action rejection in paragraph 7 inadvertantly only indicated claims 1-13, however, as discussed in last lines of page 3 and page 5, it covered the rejection of claims 1-20.

Regarding newly presented claims (80, 81, 83, 85, and 86) that are dependent on claim 1, it is noted that the steps in these claims are common to assays where biological samples, fixed and immunostained using a conjugated antibody is used in in-situ assays for determining the localization of proteins in cells and is commonly used in the art.

**Response to Applicants Arguments:**

Applicants' arguments are carefully considered, however, they are not deemed persuasive. Applicants have argued that the references of Steinier, Driever, and Weinstein do not teach using zebrafish to screen drugs, whether for angiogenic activity or otherwise. However, these arguments are not deemed persuasive because claim 1 when given broadest interpretation would include screening for any agent that affects angiogenesis and that would

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include a even a chemical mutagen which affects cardiovascular system development or angiogenesis. Additionally, studying the effect of genes discovered in the Human genome project can also be considered agents that affect angiogenesis when administered to the zebrafish and angiogenesis or cardiovascular organogenesis is studied. Regarding applicants' argument that the Stainier reference does not necessarily point out the claimed methods as to how novel differentiation based therapies will be developed, it is noted that the claimed invention is to screen for compounds that have angiogenesis activity, not therapeutic activity. Since Stainier's reference teaches studying the effect of mutagens, such as nitrosourea, on the development of cardiovascular system, it encompasses the claimed invention. It is noted that the issue is not whether using the motivation and teachings an artisan would be able to do what Applicants have done, rather the issue is whether using the motivation and teachings of the cited arts, an artisan would be able to practice the method as claimed.

8. Claims 21, 54-74, 82, 84, 87, and 88 are free of prior art.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

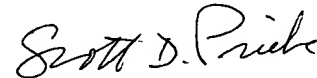
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Ram R. Shukla, Ph.D.



SCOTT D. PRIEBE, PH.D  
PRIMARY EXAMINER